

Pyridopyridazine-A Potent Pharmacophore

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ABSTRACT:

Pyridopyridazine derivatives constitute an important class of fused nitrogen-containing heterocycles that have attracted considerable interest due to their diverse biological and pharmacological profiles. The fusion of pyridine and pyridazine rings provides a rigid and electron-rich framework that contributes to their notable stability and multifunctional activity. Numerous studies have reported pyridopyridazine-based compounds exhibiting potent anticancer, antimicrobial, anti-inflammatory, antioxidant, and enzyme inhibitory effects. Recent advancements in synthetic strategies have enabled efficient and versatile routes for constructing and functionalizing the pyridopyridazine nucleus, facilitating detailed structure-activity relationship (SAR) investigations. These developments have opened new avenues for the rational design of potent and selective drug candidates. This review summarizes current progress in the synthesis, chemical reactivity, and pharmacological applications of pyridopyridazine derivatives, highlighting their significance in modern medicinal chemistry. Despite promising outcomes, further studies are required to improve their pharmacokinetic and safety profiles. Continued interdisciplinary research integrating synthetic chemistry, molecular modelling, and biological evaluation will be essential to fully exploit the therapeutic potential of this scaffold.

Key words: Pyridopyridazine, pharmacophore, anticancer, antimicrobial, anti-inflammatory.

1. INTRODUCTION

Aza-heterocycle compounds are the most promising leads in the recent decades in the treatment of many of the diseases like cancer, Alzheimer and other CNS disorders, inflammatory disorders, diabetes, hypertension, they are also used in the contagious diseases like viral, bacterial,

fungals because of their wavering physical and chemical properties and their capability in altering the metabolic pathways. Pyridine, Pyrazine, Pyrimidine, Phthalazine are the most basic and simple heterocyclic molecules containing nitrogen atoms. The presence of nitrogen atom in the molecule is responsible for their basic nature¹. Due to the vigorous research carried out in the field of diabetes, hypertension, CNS disorders now they are comparably controllable unlike the diseases caused by the enormous virus, bacteria, and fungi. These miniscule beasts are becoming stronger as they are exposed to numerous chemical compounds like antibiotics, sulfa drugs etc., rather than frail this phenomenon is collectively referred as drug resistance. These genomes are created in such a way that they can develop a resistance through various mechanisms like enzymatic inactivation, repair or amplification, intracellular localization, increased or decreased efflux. The redevelopment of the microbial resistance is so vast that the drugs given to the patient who has never been treated previously with anti microbial agents develops resistance. Various approaches have been achieved in order to overcome anti-microbial resistance such as finding out new target of activity, combination agents in order to act against more than one target site in the cell, a new delivery system to maximize the concentration of drug at the site of infection without causing any harm to the host cells².

Pyridopyridazine is the lesser known triazanaphthalene which is one of the major lead moieties in many of the drugs³. This Pyridopyridazine is formed by introduction of nitrogen atom into the benzene ring. This molecule can modify the electron distribution inside the scaffold leading to the alteration in physical and chemical properties. Rather than as an anti-microbial, Pyridopyridazine is active against various diseases amongst them it acts as protein kinase inhibitors^{14,15,16} and hence they are in the

treatment of many inflammatory diseases like rheumatoid arthritis, psoriasis, chronic obstructive pulmonary disease and hence here is the some of

the review of synthesis, and various pharmacological activities of Pyridopyridazine derivatives.

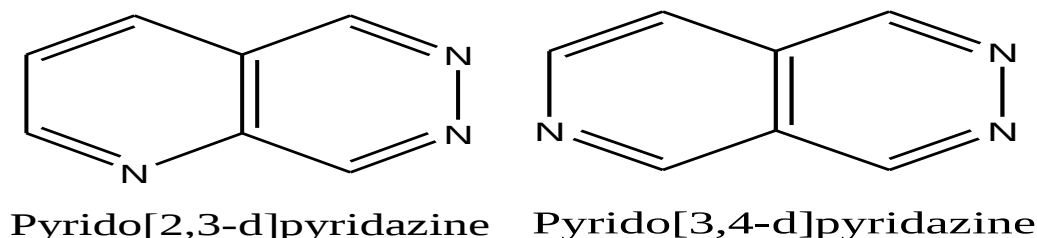


Fig 1: Pyridopyridazine

II. SYNTHESIS

Over a few decades the synthesis of Pyridopyridazine have been carried out through various methods amongst which some have been mentioned here. Pyridopyridazine and its derivatives can be synthesized by the reaction of pyridine dicarboxylic acid with hydrazine hydrate by cyclization method followed by synthesis of various derivatives via chlorination and hydrolysis to get 4-substituted pyrido[3,4-d]pyridazin-1(2H)-one derivatives and 1-substituted pyrido[3,4-d]pyridazin-4(3H)-one derivatives³. piperazine and

piperidine derivatives of Pyridopyridazine were synthesized namely (1) 4-(4-Methylpiperazin-1-yl)pyrido[3,4-d]pyridazin-1(2H)-one, (2) 4-(4-Benzylpiperazin-1-yl)pyrido[3,4-d]pyridazin-1(2H)-one, (3) 4-(4-Methylpiperidin-1-yl)pyrido[3,4-d]pyridazin-1(2H)-one, (4) 1-(4-Benzylpiperazin-1-yl)pyrido[3,4-d]pyridazin-4(3H)-one, (5) 1-(4-Methylpiperidin-1-yl)pyrido[3,4-d]pyridazin-4(3H)-one, (6) 1-(4-Benzylpiperidin-1-yl)pyrido[3,4-d]pyridazin-4(3H)-one.

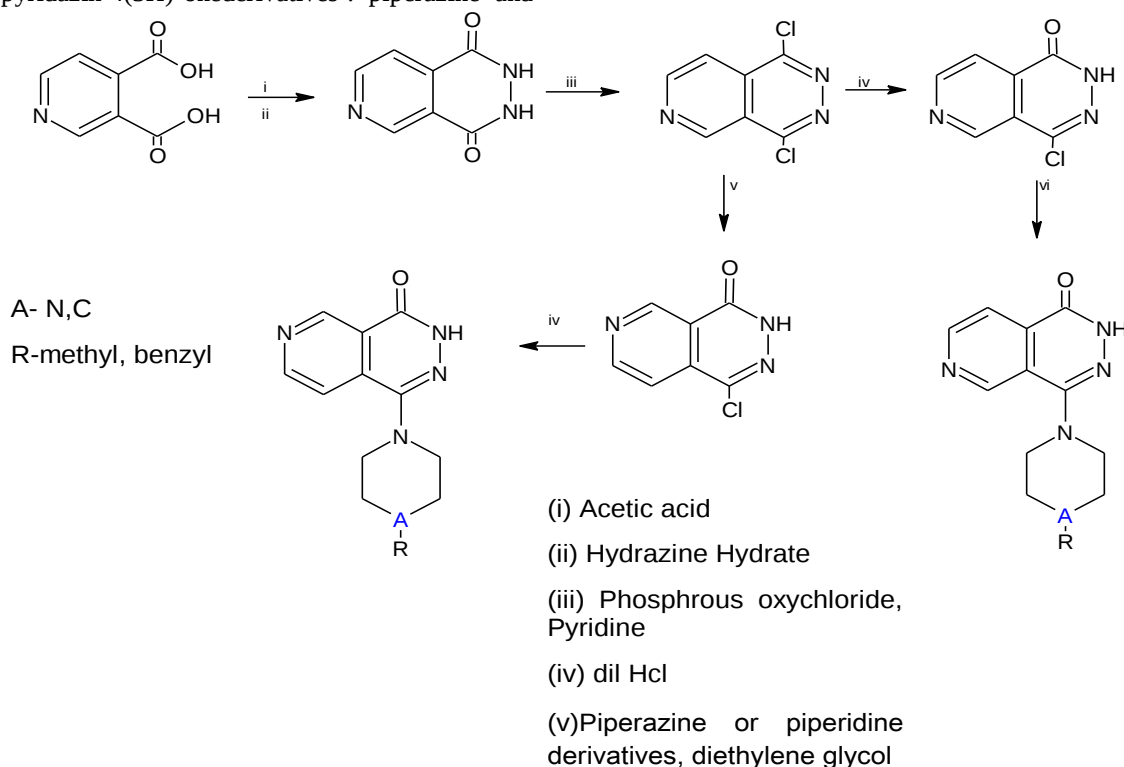
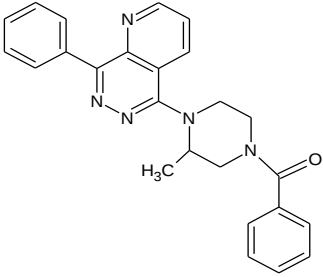
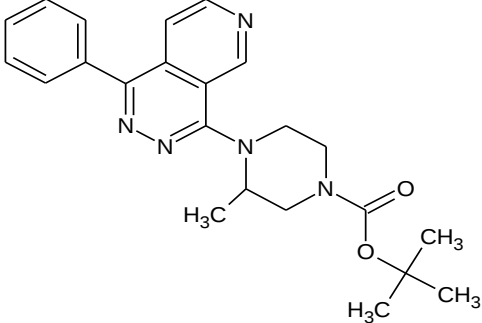
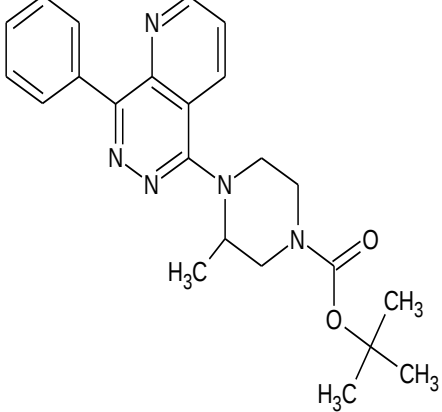
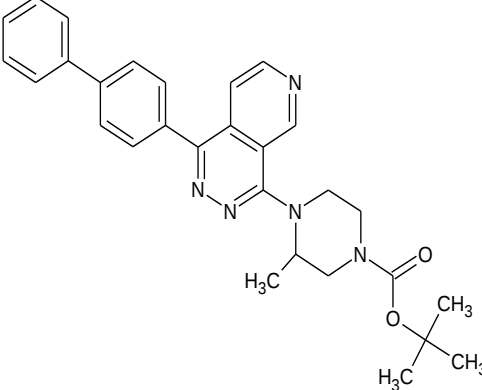


Fig 2: Synthesis Scheme of piperazine and piperidine derivatives of Pyridopyridazine

In another method, Pyridopyridazine derivatives were synthesised through previously mentioned method and the derivatives synthesized were of picoline, pyrazine, piperazine based. The starting compound here is the pyridine dicarboxylic anhydride that reacts with hydrazine and POCl_3

which then subsequently undergoes regioselective nucleophilic heteroaromatic substitution with (R)-1-benzoyl-3-methylpiperazine which then acts as the substrate for Suzuki coupling reaction⁴.

Table 1: Derivatives of Pyridopyridazine

 Compound - A	 Compound-B
 Compound-C	 Compound-D

Pyrido[2,3-d]pyridazine was synthesised by the starting material pyridone which was previously synthesized using aminoacetophenone hydrochloride.

Pyridone (**a**) was converted into its ketoester state using hydrazine hydrate and was selectively O-benzylated using silver carbonate as base in toluene which again reacts with hydrazine

hydrate to yield fused ring system (**b**) which is then deoxygenated by a chlorination/catalytic transfer hydrogenation procedure to yield (**c**). The compound (**c**) was then brominated and once in place, the bromide could be coupled in structure it was then converted to desired phenyl group and was then alkylated to required side chain to afford the coveted product (**d**)⁵.

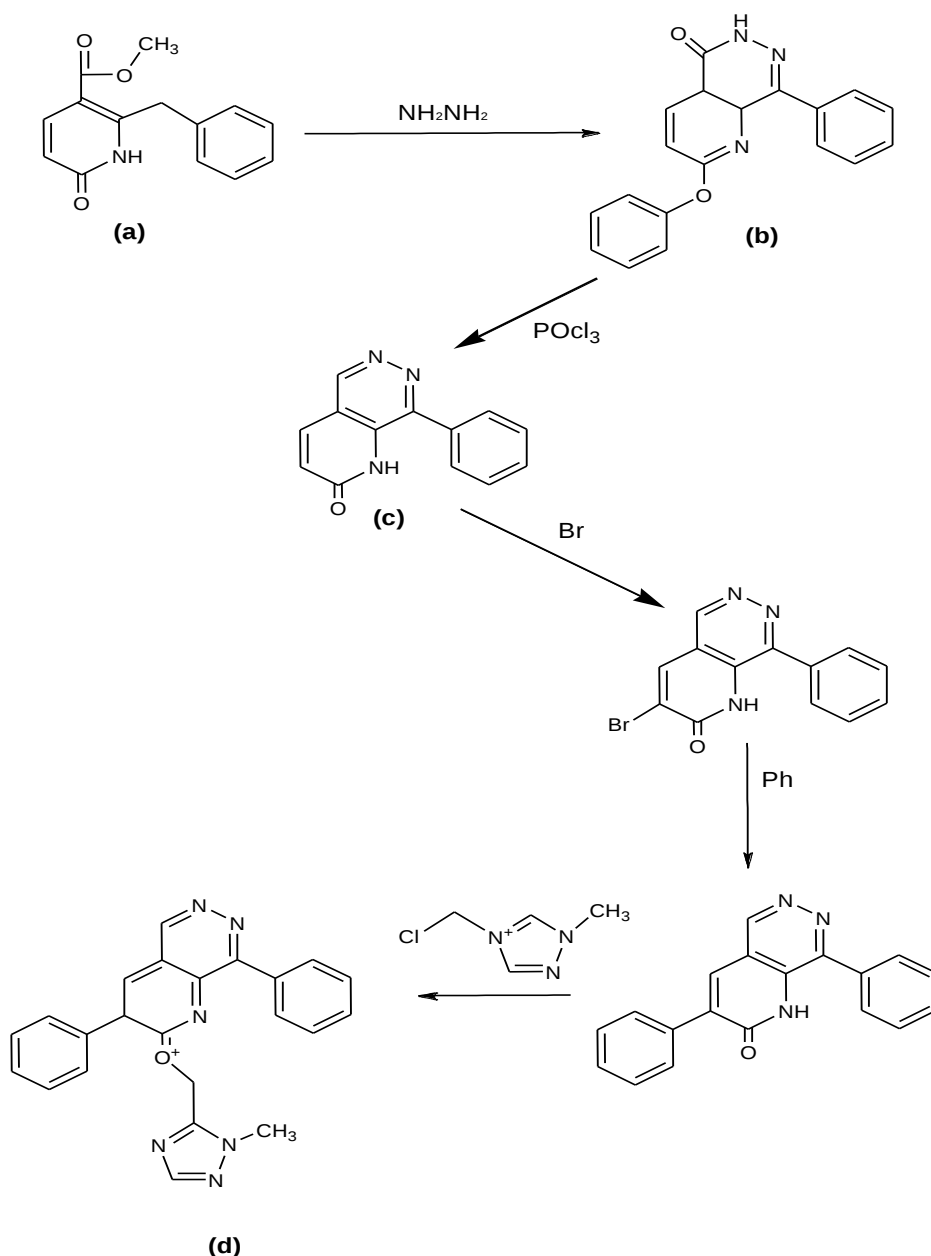


Fig 3: Synthesis of 4-amino derivatives of pyrido[3,4-d]pyridazine

Keto form of pyridopyridazine was synthesized by converting aminoacetonitrile hydrogensulfate into the Schiff's base by reacting with the aldehyde in a basic medium which then undergoes cycloaddition reaction with dimethylacetylenedicarboxylate to give the pyridine derivative. The obtained product then undergoes reaction with hydrazine hydrate in ethanol yields Pyridopyridazine with the loss of two molecules of methanol⁷. N-arylpiperazinylalkyl

derivatives of 1,4-dioxo(1,4,5-trioxo) - 1,2,3,4- & (1,2,3,4,5,6-hexa) hydroxyrido[3,4-d] pyridazines where the starting material is 2,6,7-trimethyl-1,4,5-trioxo-1,2,3,4,5,6-hexahydroxyrido[3,4-d] pyridazine which upon reacting with POCl_3 yields 4-chloro-2,6,7-trimethyl-1,5-dioxo-1,2,5,6-tetrahydroxyrido[3,4-d] pyridazine which upon treated with amino acids to give corresponding 4-amino derivatives of pyrido[3,4-d]pyridazine⁸.

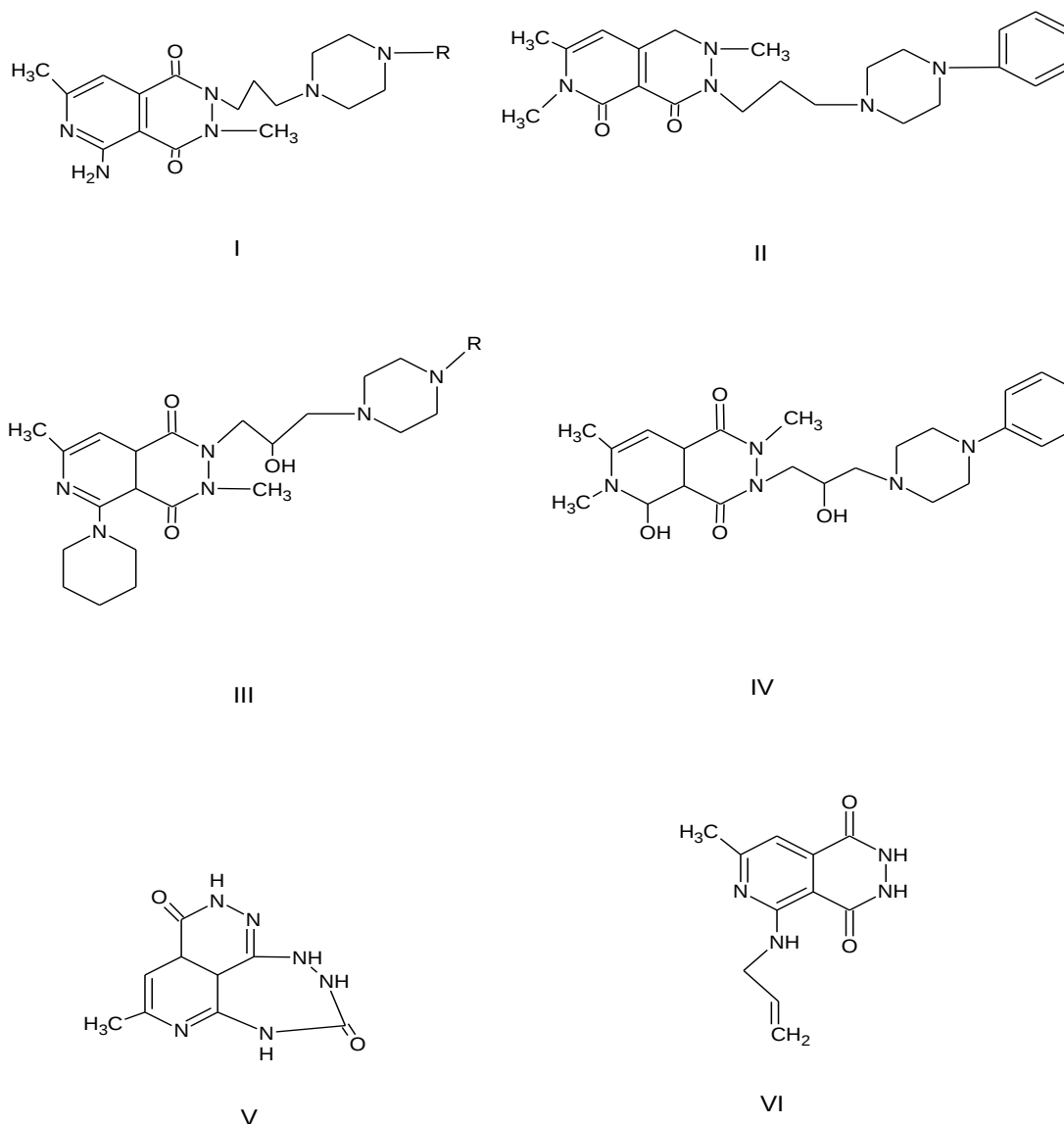


Fig 4: 4-amino derivatives of pyrido[3,4-d]pyridazine

Where for the structure (I) R is methylbenzene and 1-chloro-2-methyl benzene for the structure (III) R is methylbenzene and 2-methylpyrimidine.

III. PHARMACOLOGICAL ACTIVITIES

Many pharmacological activities have been studied among which some of them are mentioned.

3.1. Anti-hypertensive

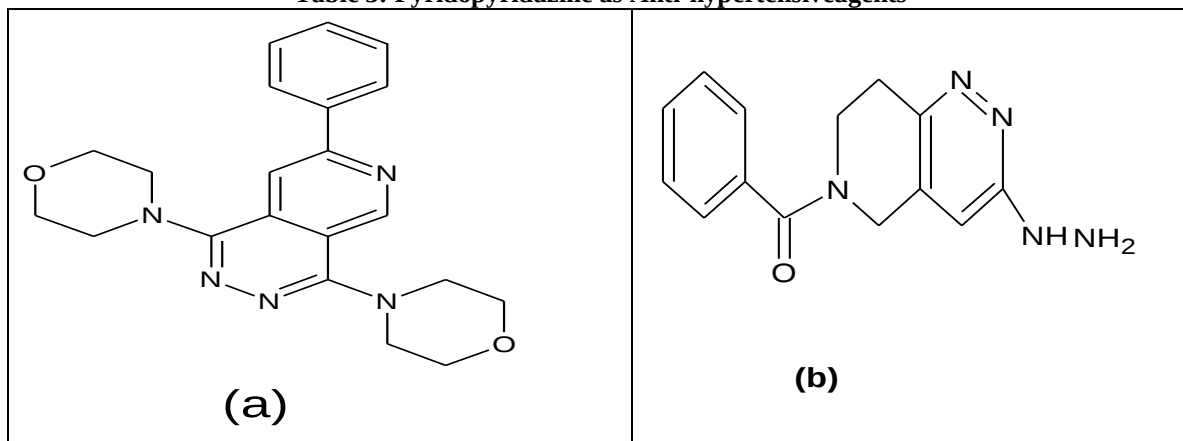
Hypertension is one of the serious health issues that caused by the prolonged exertion of

force by the blood towards the inner walls of arteries that may cause various diseases like cardiac failure. Some of the Pyridopyridazine derivatives are used for the treatment of hypertension among which compound (a) and (b) shows the maximum antihypertensive activity⁹. Compound Endralazine¹⁰(b) is one amongst the major antihypertensive agent of pyridopyridazine. The activity of the compound was studied by comparing with Dihydralazine. The results were described briefly;

Table 2: Anti-hypertensive activity of the Pyridopyridazine derivatives

Endralazine					Dihydralazine				
Treatment period	Placebo	Week 1	Week 2	Week 3	Week 6	Week 1	Week 2	Week 3	Week 6
Systolic pressure Mean (mmHg)	216	167	162	159	148	172	166	168	153
Diastolic pressure Mean (mmHg)	130	106	103	100	92	109	106	106	97
Heart rate Mean (beats/min)	85	78	74	74	74	71	72	73	72

Table 3: Pyridopyridazine as Anti-hypertensive agents



3.2. Anti-Diabetic

In a normal person glucose is converted in to Sorbitol by Aldose reductase in the presence of NADPH. In the tissues that shows diabetes pathology the aldose reductase is directly competed by hexokinase for the utilization of glucose. The affinity of aldose reductase towards glucose is comparably less than that of hexokinase. So that under normal physiological condition the glucose is rapidly phosphorylated by hexokinase. In diabetes mellitus the accumulation of glucose causes the saturation of hexokinase so that large amount of sorbitol is produced which accumulates as a fructose. Due to the high polarity of the alcohol group present in the fructose it makes difficult in

the diffusion from the cell membrane. Which in turn causes the hyper osmotic effect which causes the infusion of fluid inside the cell. This is called sorbitol pathway¹¹. Due to the presence of nitrogen atoms pyridopyridazine is best in its basicity and polarity. The higher basicity is considered to be most appropriate to synthesise ARIs as they have to penetrate in to the difficultly accessible tissues. The nitrogen of the pyridine which at the α position to the carbonyl /imine functional group would be non basic and the backbones containing alternative nitrogens shows higher basicity hence the study suggests that the pyridopyridazinones has replaced phthalazinone for the design of potent ARIs. The results has been elaborated in table 2.

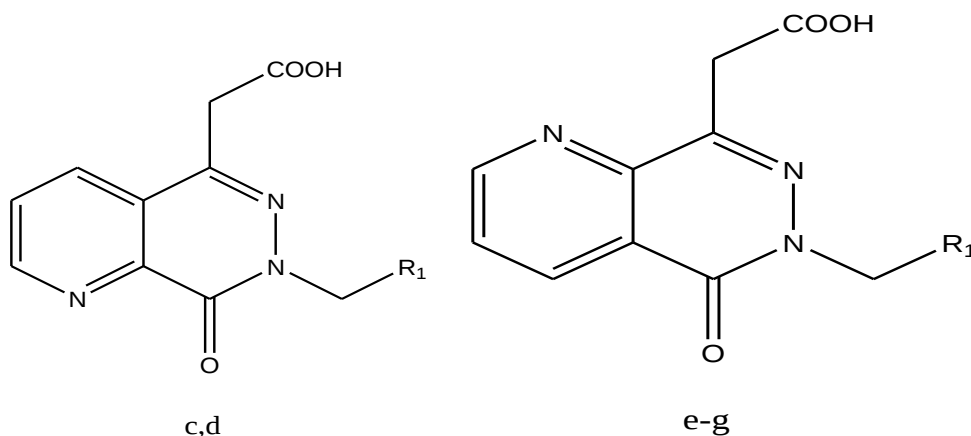


Fig 5: Pyridopyridazine derivatives as Anti-Diabetic

Table 4: Anti-Diabetic activity of Pyridopyridazine derivatives

R ₁	IC ₅₀ , ^a M	Dose (mg/kg)	% inhibition
4-Br-2-F-phenyl	7.6×10^{-7}	25	NS
5-CF ₃ -2-benzothiazolyl	2.1×10^{-7}	10	NS
5-F-2benzothiazolyl	$<10^{-8d}$	25	64
5-CF ₃ -2-benzothiazolyl	4.1×10^{-8}	25	74
5,7-F ₂ -2-benzothiazolyl	2.6×10^{-8}	25	68

3.3. CNS disorders

GABA_A receptors are the main metabotropic as well as G protein coupled receptors which are chief respond sites for neurotransmitter – gamma aminobutanic acid(GABA). GABA receptors are the main cause associated with the disorders like anxiety, convulsions or cognitive

disorders. Pyrido-(2,3-c)pyridazine analogues which are Substituted in the 4-position by a Substituted phenyl ring acts as a ligand for GABA_A receptors and hence they are used in the treatment of above-mentioned diseases. These derivatives possess a greater affinity towards $\alpha 2, \alpha 3, \alpha 5$ subunits of GABA receptors¹².

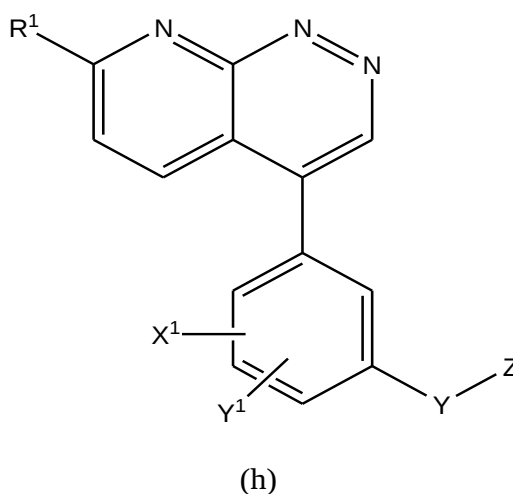
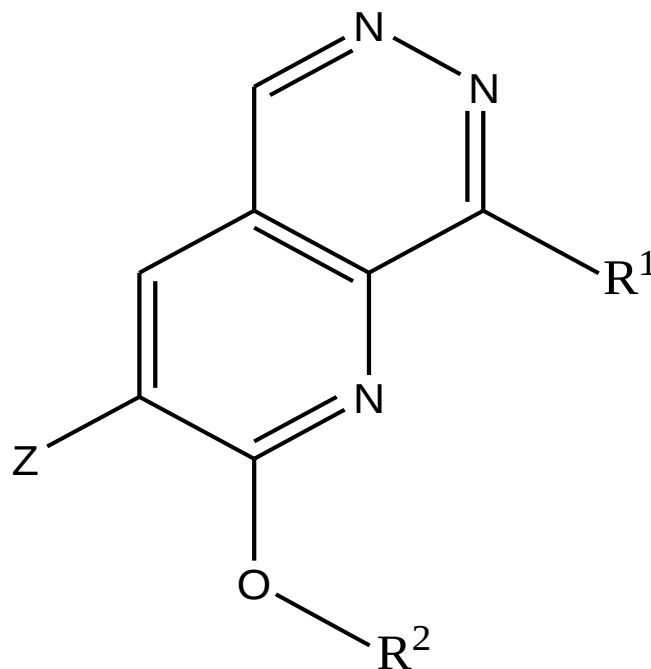


Fig 6: Pyridopyridazine derivatives as Anti-convulsive

Where,

- X^1 represents hydrogen, halogen, C_{1-6} alkyl, trifluoromethyl or C_{1-6} alkoxy.
- Y^1 represents hydrogen or halogen
- Y represents a chemical bond, an oxygen atom, or a —NH-linkage
- Z represents an optionally substituted aryl or heteroaryl
- Group, R^1 represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro etc.



(i)

Fig 7: Pyridopyridazine derivatives as Anti-Anxiety agents

Compound (i) also acts as a $GABA_A$ receptor ligands

Where,

- Z represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, C_{6-8} bicycloalkyl, aryl, C_{3-7} heterocycloalkyl, heteroaryl or di(C_{1-6})alkylamino, any of which groups may be optionally Substituted.
- R^1 represents C, cycloalkyl, phenyl, furyl, thienyl or pyridinyl, any of which groupS may be optionally Substituted
- R represents C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally Substituted.

3.4. Anticancer

One of the leading deaths causing disease in the present world is Cancer. Though the causes for cancer are numerous, the treatment aids are still lacking behind with only few types namely radiotherapy, chemotherapy with their highest adverse effects. In recent years many chemical compounds have been identified for their anti cancer activity they are also shows their adverse effects on other healthy cells making them unfit for the treatment. The synthesized few pyridopyridazine derivatives which shows anticancer activities. The activity have been tested on human breast adenocarcinoma (MCF-7) cells that shows moderate to good effect against Doxorubicin, a potent anticancer agent as a standard drug¹³.

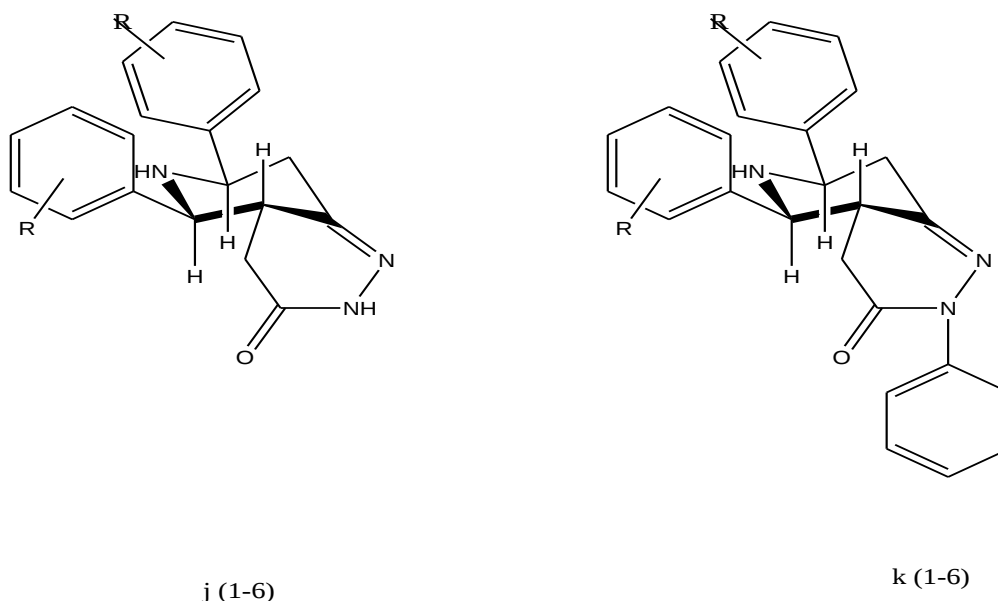


Fig 8: Pyridopyridazine derivatives as Anti-Cancer agents

Table 5: Anti-cancer activity of Pyridopyridazine derivatives

Compound	R	MCF-7 IC ₅₀ ^a (μM)
J1	H	475.4 ± 27.8
J2	CH ₃	498.4 ± 30.0
J3	OCH ₃	344.1 ± 59.4
J4	Cl	61.3 ± 5.8
J5	Br	78.9 ± 14.7
J6	3-NO ₂	141.0 ± 22.5
K1	H	268.7 ± 15.4
K2	CH ₃	219.0 ± 11.0
K3	OCH ₃	248.1 ± 17.2
K4	Cl	364.1 ± 20.2
K5	Br	810.0 ± 35.7
K6	3-NO ₂	473.7 ± 26.1
Doxorubicin		2.007 ± 0.05

(Inhibitory concentration (IC₅₀, μM) as obtained from MTT assay. All the values represent the average of three experimental samples. The cells were incubated for a period of 48 h).

3.5. Anti-microbial agent

Antibacterial, antifungal and antimycobacterial activity has been studied for the pyridopyridazine derivatives that are

synthesized. The compounds synthesized were 1/4 – Benzylpiperazine/Benzylpiperidine derivatives of pyridopyridazine⁴. The synthesis regarding the compounds were mentioned in the synthesis section of this article. Among which 1-(4-Benzylpiperazin-1-yl)pyrido[3,4-d]pyridazin-4(3H)-one and 1-(4-Benzylpiperidin-1-yl)pyrido[3,4-d]pyridazin-4(3H)-one shows the higher effectiveness towards microbes.

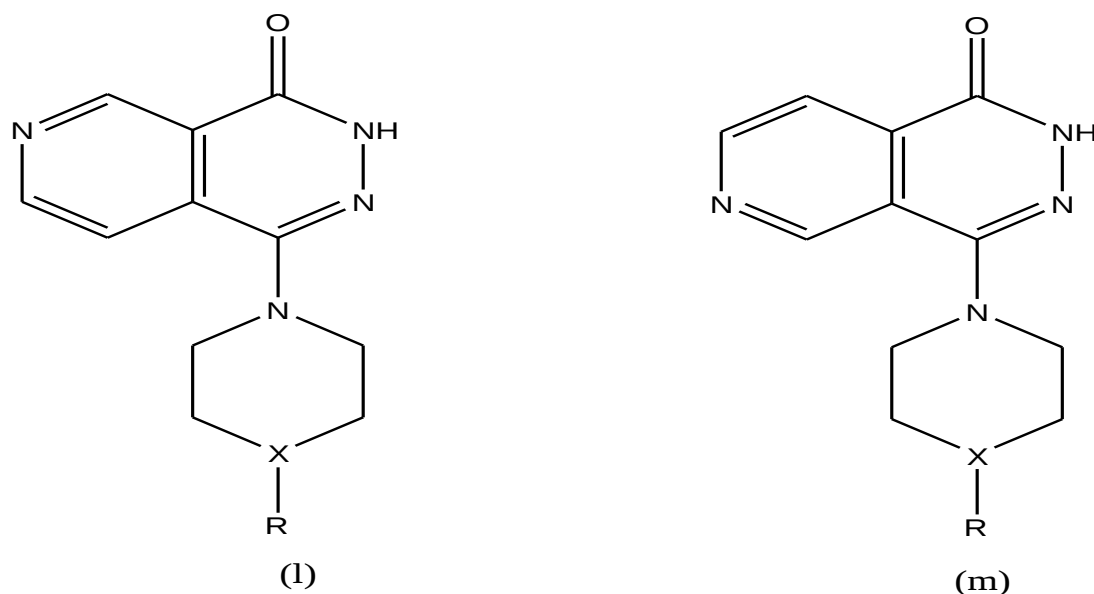


Fig 9: Pyridopyridazine derivatives as Anti-Microbial agents

IV. CONCLUSION

Pyridopyridazine derivatives have emerged as a versatile class of heterocyclic compounds with significant potential across diverse pharmacological and chemical applications. The unique fused bicyclic framework of the pyridopyridazine nucleus contributes to its remarkable stability and broad spectrum of biological activities, including anticancer, antimicrobial, anti-inflammatory, and enzyme inhibitory properties. Advances in synthetic methodologies have enabled efficient functionalization of this scaffold, facilitating structure–activity relationship (SAR) studies and optimization of bioactive analogues. Despite the progress achieved, further exploration is warranted to fully harness the therapeutic potential of pyridopyridazine derivatives. Future research should focus on rational drug design, molecular docking, and in vivo evaluations to better understand their mechanisms of action and pharmacokinetic profiles. With continued interdisciplinary efforts integrating synthetic chemistry, computational modeling, and biological screening, pyridopyridazine-based compounds hold strong promise as lead candidates for the development of novel therapeutic agents.

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